BLOOD PRESSURE ELEVATION:
IMPACT ON CARDIOVASCULAR STRUCTURE AND ENDOGENOUS FIBRINOLYSIS

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Abstract:

Blood pressure elevation is a major risk factor for cardiovascular events and the risk increases in a dose-dependant manner. It is of importance to identify subjects prone to develop hypertension and adverse cardiovascular remodeling in order to start treatment timely. The increased risk of myocardial infarction and ischemic stroke in hypertension suggests that the condition is associated with prothrombotic mechanisms. Our research group recently discovered that the capacity for activation of the endogenous fibrinolytic system by acute release of tissue plasminogen activator (t-PA) is markedly impaired in subjects with hypertension. This impairment could contribute to the increased risk for atherothrombotic events.

The predictive value of blood pressure elevation (SBP 140-160 and/or DBP 85-95 mmHg; BPE group) or normal blood pressure (SBP 110-130 and DBP 60-80 mmHg; NC group) was studied in a cohort of 20-year old men investigated in 1987. The prevalence of hypertension was 74.5% and 5.9% in the BPE and NC group, respectively, at 20 year follow-up. The difference in blood pressure level at baseline between the groups contrasted even more at follow-up. Further, the BPE group had significantly increased left ventricular mass index and intima-media thickness compared to the NC group.

We investigated if the impaired fibrinolytic capacity in untreated hypertension could be restored by chronic and acute blood pressure lowering. T-PA release was stimulated by infusion of substance P in the perfused-forearm model before and during chronic and acute blood pressure lowering. Chronic antihypertensive treatment with either the calcium antagonist felodipine or the ACE-inhibitor lisinopril, increased the amount of t-PA released and improved the rapidity of the t-PA response. Changes were similar in the two treatment groups, suggesting the improvement to be related to the blood pressure lowering *per se*. However, acute blood pressure lowering with intravenous sodium nitroprusside did not affect the stimulated t-PA release. The results of the two studies indicate that high blood pressure decreases the cellular content of t-PA, rather than interfering with the release mechanisms of the protein.

Further, we explored the impact of the tensile force component of blood pressure on the regulation of fibrinolytic proteins by studying cultured endothelial cells in an *in vitro* biomechanical experimental model. Prolonged cyclic strain, mimicking the hypertensive state, was found to suppress t-PA gene expression and protein secretion. In contrast, the main inhibitor of t-PA, plasminogen activator inhibitor-1 was induced, adding to the negative effects of elevated blood pressure on fibrinolysis.

In conclusion, blood pressure elevation in young age predicts adverse cardiovascular remodeling and hypertension twenty years later. Hypertension increases the risk of atherothrombotic events by impaired fibrinolysis, possibly through a direct inhibitory effect on t-PA expression by enhanced tensile stress. Chronic blood pressure lowering restores the endogenous fibrinolytic capacity, and this could contribute to the beneficial effect of anti-hypertensive therapy.

Key words: hypertension, left ventricular hypertrophy, intima-media thickness, fibrinolysis, endothelium, tissue plasminogen activator, antihypertensive agents, mechanical stress, plasminogen activator inhibitor-1

ISBN 978-91-628-7487-2

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Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Centralklinikens aula, Sahlgrenska universitetssjukhuset/Östra, torsdagen den 5 juni 2008 kl 09.00

av

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Professor Lars Lind
Akademiska sjukhuset, Uppsala

This thesis is based on the following papers:

I Ridderstråle W, Saluveer O, Johansson M, Bergbrant A, Jern S, Hrafnkelsdóttir TJ.
Consistency of blood pressure and impact on cardiovascular structure over 20 years in young men.
Manuscript.

II Ridderstråle W, Ulfhammer E, Jern S, Hrafnkelsdóttir T.
Impaired capacity for stimulated fibrinolysis in primary hypertension is restored by antihypertensive therapy.
Hypertension 2006;47:686-91.

III Ridderstråle W, Saluveer O, Carlström M, Jern S, Hrafnkelsdóttir TJ.
The impaired fibrinolytic capacity in hypertension is not improved by acute blood pressure lowering.
Submitted.

IV Ulfhammer E, Ridderstråle W, Andersson M, Karlsson L, Hrafnkelsdóttir T, Jern S.
Prolonged cyclic strain impairs the fibrinolytic system in cultured vascular endothelial cells.
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Göteborg 2008

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